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KIR gene content diversity in four Iranian populations

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Abstract Killer cell immunoglobulin-like receptors (KIR) regulate natural killer cell response against infection and malignancy. *KIR* genes are variable in the number and type, thereby discriminating individuals and populations. Herein, we analyzed the *KIR* gene content diversity in four native populations of Iran. The *KIR* genomic diversity was comparable between Bakhtiari and Persian and displayed a balance of A and B *KIR* haplotypes, a trend reported in Caucasian and African populations. The *KIR* gene content profiles of Arab and Azeri were comparable and displayed a preponderance of B haplotypes, a scenario reported in the natives of America, India, and Australia. A majority of the B haplotype carriers of Azeri and Arab had a centromeric gene-cluster (*KIR2DS2-2DL2-2DS3-2DL5*). Remarkably, this cluster was totally absent from the American natives but occurred at highest frequencies in the natives of India and Australia in combination with another gene cluster at the telomeric region (*KIR3DS1-2DL5-2DS5-2DS1*). Therefore, despite having similar frequencies of B haplotypes, the occurrence of B haplotype-specific *KIR* genes, such as *2DL2*, *2DL5*, *3DS1*, *2DS1*, *2DS2*, *2DS3*, and *2DS5* in Azeri and Arab were substantially different from the natives of America, India, and Australia. In conclusion, each Iranian population exhibits distinct *KIR* gene content diversity, and the Indo-European *KIR* genetic signatures of the Iranians concur with geographic proximity, linguistic affinity, and human migrations.

Keywords NK cells · *KIR* genes · Immunity-related genes · Polymorphism · Iranian populations · Persian

Introduction

Natural killer (NK) cells are fast-acting lymphocytes that provide the first line of defense against infection and tumor transformation (Trinchieri 1989). Human NK cells largely use killer cell immunoglobulin-like receptors (KIR) to distinguish the unhealthy targets from the healthy self (Lanier 2005). A family of 16 homologous genes clustered at the leukocyte receptor complex on chromosome 19q13.4 encodes KIR receptors (Vilches and Parham 2002; Wilson et al. 2000). Fourteen of them encode receptors that trigger either inhibition (3DL1-3, 2DL1-3, and 2DL5) or activation (3DS1, 2DS1-2DS5) or both (2DL4) and two pseudogenes (*2DP1* and *3DP1*) that do not encode a cell-surface receptor. The inhibitory KIRs recognize distinct motifs of HLA class I molecules and trigger signals that stop NK cell function, while the ligands for the activating KIRs are unknown. Epidemiological studies suggest that the activating KIRs may recognize pathogen-derived or pathogen-induced

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cell surface determinants and trigger NK response against the unhealthy targets, which may yield immunopathology or resistance to infection (Khakoo and Carrington 2006).

The number and type of *KIR* genes vary substantially between haplotypes and display sequence polymorphism (Hou et al. 2008; Hsu et al. 2002; Martin et al. 2004; Middleton et al. 2007; Shilling et al. 2002; Whang et al. 2005; Wilson et al. 2000). On the basis of gene content, *KIR* haplotypes are broadly classified into two groups (Uhrberg et al. 1997). Group A haplotypes have a fixed gene content comprising *KIR3DL3-2DL3-2DP1-2DL1-3DP1-2DL4-3DL1-2DS4-3DL2* but are diversified through allelic polymorphism of the individual genes. In contrast, group B haplotypes have variable gene content comprising several genes and alleles that are not part of the A haplotype. Particularly, *KIR2DS1*, *2DS2*, *2DS3*, *2DS5*, *2DL2*, *2DL5*, and *3DS1* are associated only with group B haplotypes, and thus B haplotypes generally encode more activating KIR receptors than the A haplotype that encodes a single activating receptor, KIR2DS4. Four framework genes (*KIR3DL3*, *3DP1*, *2DL4*, and *3DL2*) are conserved on both A and B haplotypes and therefore ubiquitously present in all individuals.

All human populations have both group A and B haplotypes, but their frequencies vary considerably (Parham 2005; Single et al. 2007; Yawata et al. 2002a). In Africans and Caucasians, the A and B haplotypes are equally distributed, suggestive of a balancing selection. Conversely, the A haplotype is overrepresented in Northeast Asians (Chinese, Japanese and Koreans), while the *B* haplotype occurred most frequently in the natives of India, Australia, and America (Ewerton et al. 2007; Flores et al. 2007; Gendzekhadze et al. 2006; Jiang et al. 2005; Norman et al. 2002; Rajalingam et al. 2002; Toneva et al. 2001; Whang et al. 2005; Yawata et al. 2002b). Herein, we investigated the *KIR* gene content diversity in four native populations of Iran, a country with central geographic location which served as a gateway of human movements during the past 60,000 years.

Materials and methods

Study subjects and DNA extraction

A total of 504 unrelated individuals belonging to four native populations of Iran were included in this study (Fig. 1). Persian people (n=248), who speak Persian as their primary language, live in Fars province. Azeri people (n=84) live in East Azerbaijan province and speak Turkic language. Bakhtiari people (n=96) live in Khuzestan province and speak Luri, a dialect of Persian language. Arab people (n=76) live in Khuzestan province and speak

Fig. 1 Map of Iran showing the provinces of four study populations. DNA samples of Persian population were collected from Fars province, Azeri were collected from East Azerbaijan province, and Bakhtiari and Arab were collected from Khuzestan province

Arabic. The study was reviewed and approved by the appropriate Institutional Review Boards of human research protection. Genomic DNA was extracted from peripheral blood samples using either standard salting out method or by QIAamp blood kit (Qiagen, Hilden, Germany). The quality and quantity of DNA samples were determined by UV spectrophotometry, and the concentration was adjusted to 100 ng/μL.

KIR genotyping

The presence and absence of 16 distinct *KIR* genes was determined using our recently developed duplex sequence-specific priming-based polymerase chain reaction (SSP-PCR) typing system (Ashouri et al. 2009). The unique and unusual *KIR* genotypes were further confirmed by re-typing using our alternative SSP-PCR typing method (Du et al. 2007). Both of the typing methods were validated extensively using the UCLA International KIR exchange reference DNA samples, which provided identical *KIR* genotyping results, indicating that the specificity and sensitivity of the two methods were comparable (Ashouri et al. 2009).

The *KIR* genotyping data of world populations used for comparison in this study was extracted from the following publications: Han Chinese (Jiang et al. 2005), Korean (Whang et al. 2005), Japanese (Yawata et al. 2002b), Vietnamese, Australian Aborigine (Toneva et al. 2001), Thai, British Caucasian, Palestinian Arab (Norman et al. 2001), Warao, Bari, Yucpa (Gendzekhadze et al. 2006), Australian Caucasian (Witt et al. 1999), New York Caucasian (Hsu et al. 2002), Finnish, French Caucasian, Senegal African,

Guadeloupe Caribbean, and Reunion, a population from Indian Ocean origin (Denis et al. 2005), American Caucasian, Hispanic, African American (Du et al. 2007), Greek (Niokou et al. 2003), Afro-Caribbean, Trinidad Asian, Pakistani (Norman et al. 2002), North Indian (Rajalingam et al. 2002), Chinese, Malay and Indian migrants in Singapore (Lee et al. 2008), Parsi and Maharastrian of India (Kulkarni et al. 2008), Paravar, Kanikar, Mollukurumba (Rajalingam et al. 2008), Basque population (Santin et al. 2006), Cook Island, Samoan, Tokelau, Tongan (Velickovic et al. 2006), Mestizo, Huichol, Purepecha, Tarahumara (Gutierrez-Rodriguez et al. 2006), Northern Irish (Middleton et al. 2007), Wichis and Chiriguanos (Flores et al. 2007), and Amazonian Amerindian (Ewerton et al. 2007).

Prediction of haplogroups from genotypes

KIR gene content of a given individual is conventionally called "*KIR* genotype," which is variable among individuals. The *KIR* gene content was used to infer group A and B *KIR* haplotypes and to assign each person to one of three genotypes: AA, BB, and AB. Individuals having only genes of the group A *KIR* haplotypes (*KIR3DL3-2DL3-2DL1-2DP1-3DP1-2DL4-3DL1-2DS4-3DL2*) were considered to be homozygous for the A haplotype and assigned the *KIR* genotype AA. Individuals lacking any of the four A haplotype associated genes (*KIR2DL1, 2DL3, 3DL1*, and *2DS4*) that have a known function and vary among individuals in their existence were regarded to be homozygous for group B haplotypes and assigned the *KIR* genotype BB. All other individuals were regarded to be heterozygous for A and B haplotypes and assigned the *KIR* genotype AB. The individuals with AB genotypes had all nine genes present on the A haplotype, as well as one or more B haplotype specific genes (*2DL2*, *2DL5*, *2DS1*, *2DS2*, *2DS3*, *2DS5*, and *3DS1*). The AB and BB genotypes were previously referred together as *KIR* genotype Bx (McQueen et al. 2007).

Classification of genotypes on the basis of centromeric and telomeric gene clusters

Based on the linkage disequilibrium, we recognized two frequently occurring gene clusters (Du et al. 2008). One cluster comprises *KIR2DS2-2DL2-2DS3-2DL5* genes and is

Table 1 Comaprison of carrier frequency of *KIR* genes in four Iranian populations

KIR	Persian (Per) *n*=248	Bakhtiari (Bak) *n*=96	Arab (Arb) *n*=76	Azeri (Aze) *n*=84	*p* values					
					Per vs. Bak	Per vs. Arb	Per vs. Aze	Bak vs. Arb	Bak vs. Aze	Arb vs. Aze
	%F (*N*)	%F (*N*)	%F (*N*)	%F (*N*)						
A haplotype associated *KIR* genes										
2DL1	98.0 (244)	94.8 (91)	100 (76)	98.0 (83)						
2DL3	91.0 (226)	89.6 (86)	89.5 (68)	89.2 (75)						
3DL1	94.0 (238)	95.8 (92)	85.5 (65)	90.5 (76)						
2DS4	96.0 (239)	97.9 (94)	98.7 (75)	98.8 (83)						
B haplotype associated *KIR* genes										
2DL2	56.8 (141)	54.1 (52)	63.1 (48)	67.9 (57)						
2DL5	58.0 (144)	54.1 (52)	67.1 (51)	73.8 (62)			0.013		0.0083	
3DS1	33.0 (83)	45.8 (44)	42.1 (32)	38.0 (32)	0.035					
2DS1	35.0 (89)	42.7 (41)	44.7 (34)	39.2 (33)						
2DS2	54.0 (135)	49.0 (47)	56.3 (49)	70.2 (59)			0.015	0.046	0.0041	
2DS3	38.3 (95)	27.1 (26)	50.0 (38)	53.5 (45)			0.015	0.0025	0.0004	
2DS5	25.4 (63)	39.6 (38)	35.5 (27)	34.5 (29)	0.012					
Framework genes/pseudogenes										
2DL4	100 (248)	100 (96)	100 (76)	100 (84)						
3DL2	100 (248)	100 (96)	100 (76)	100 (84)						
3DL3	100 (248)	100 (96)	100 (76)	100 (84)						
2DP1	98.0 (243)	96.9 (93)	98.7 (75)	100 (84)						
3DP1	100 (248)	100 (96)	100 (76)	100 (84)						

Frequency (%F) of carriers of each gene is expressed as a percentage and defined as the number of individuals carrying the gene (*N*) divided by the number of individuals studied (*n*) in the given population group. The *p* values are given only for those pairwise comparisons indicating significant (<0.05) differences

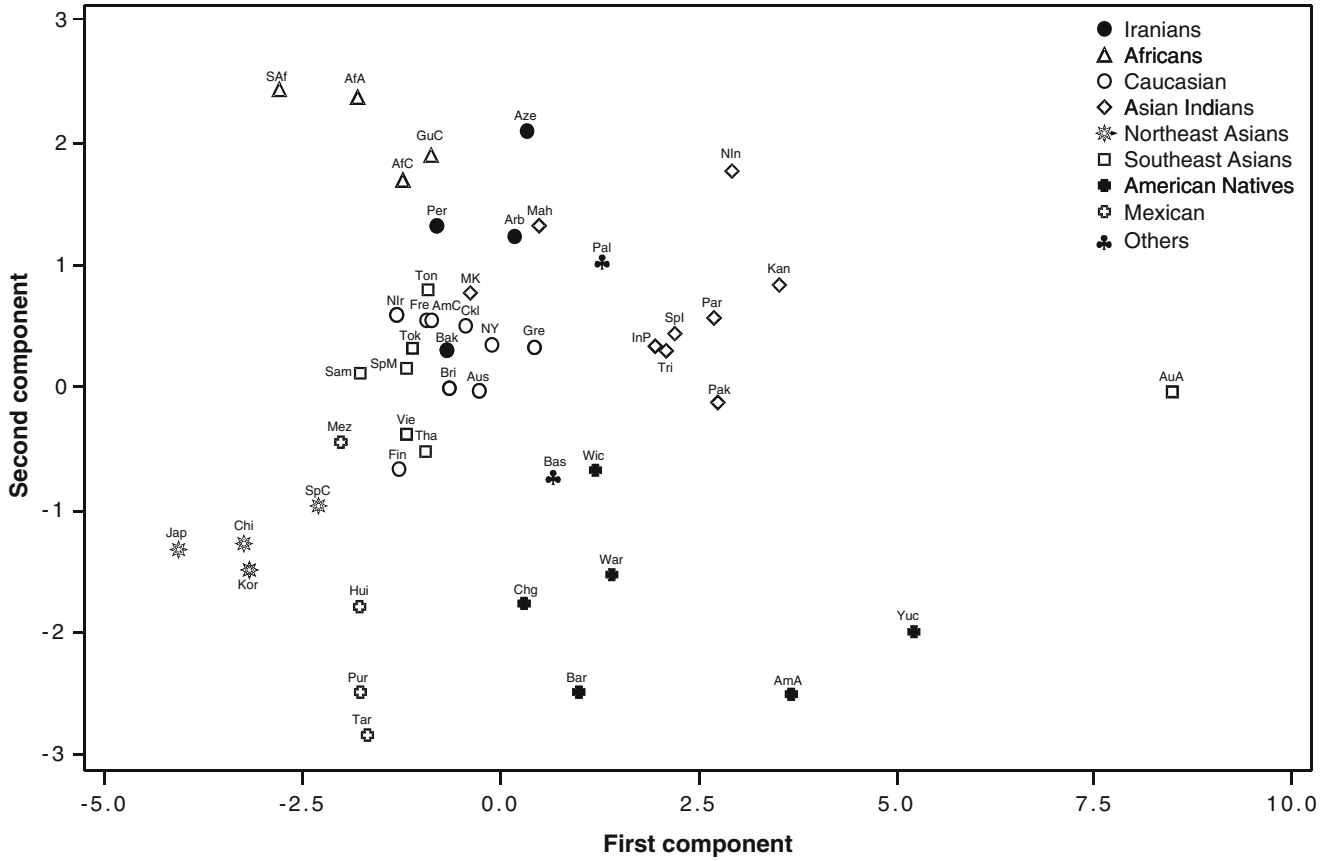

Fig. 2 Principal component analysis (PCA) of carrier frequency of nine variable *KIR* genes. The PCA graph built upon the frequencies of individuals carrying nine variably occurring *KIR* genes (*2DL1-3*, *2DS1-4*, *3DL1*, and *3DS1*) shows a global view relationship between the four Iranian populations studied in this paper and other previously reported world populations. The other seven genes (*2DL5*, 2DS5, *2DL4*, *3DL2*, *3DL3*, *2DP1*, and *3DP1*) were excluded from the analysis because they were either invariably present in all individuals or not typed in some populations. *Jap* Japanese, *Chi* Han Chinese, *Kor* Korean, *SpC* Singapore Chinese, *Hui* Huichol, *Pur* Purepecha, *Tar* Tarahumara, *Chg* Chiriguanos, *Wic* Wichis, *War* Warao, *Bar* Bari, *AmA* Amazonian Amerindian, *Yuc* Yucpa, *Vie* Vietnamese, *Tha* Thai, *Reu* Reunion, *Gre* Greek, *CkI* Cook Island, *Sam* Samoan, *Tok* Tokelau, *Ton* Tongan, *Mez* Mestizo, *Bri* British Caucasian, *Aus* Australian Caucasian, *NIr* Northern Irish, *NY* New York Caucasian, *Fin* Finnish, *Fre* French Caucasian, *AmC* American Caucasian, *SpM* Singapore Malay, *His* Hispanic, *MK* Mollukurumba, *SAf* Senegal African, *GuC* Guadeloupe Caribbean, *AfA* African American, *AfC* Afro-Caribbean, *Per* Persian, *Bak* Bakhtiari, *Arb* Iranian Arab, *Aze* Azeri, *Pal* Palestinian Arab, *Mah* Maharashtrian, *Tri* Trinidad Asian, *Pak* Pakistani, *NIn* North Indian, *Par* Paravar, *Kan* Kanikar, *InP* Indian Parsi, *Bas* Basque population, *SpI* Singapore Indians, *AuA* Australian Aborigine

located at the centromeric half of the *KIR* gene complex, while another cluster comprises *KIR3DS1-2DL5-2DS1-2DS5* genes and is located at the telomeric half of the complex. For simplicity, we call these clusters C4 and T4, in which "C" represents centromeric, "T" represents telomeric, and "4" indicates the number of genes. On the basis of the presence and absence of C4 and T4 clusters, the Bx genotypes were further divided into the following four subsets: C4Tx (presence of C4 and absence of T4), CxT4 (absence of C4 and presence of T4), C4T4 (presence of both C4 and T4), and CxTx (absence of both C4 and T4). These Bx subsets were substantially variable in activating *KIR* gene content.

Fig. 3 *KIR* gene content diversity of Iranian populations. Within 504 unrelated individuals representing four linguistic Iranian populations, 78 genotypes that differed by the presence (*shaded box*) and absence (*white box*) of 16 *KIR* genes were observed. The frequency of each genotype is presented in percentage frequency (%F) and defined as the number of individuals carrying the genotype (*N*) divided by the number of individuals studied (*n*) in the given population. Genotypes with identical gene content listed in this figure and in the Supplementary Figure 1a, b are marked with the same number. Unique genotypes that were not reported from other ethnic populations are identified by *asterisk*. Based on the gene content, genotypes were grouped as we described in the text. The genotypes that significantly differed ($p<0.05$) among Iranian populations are marked by *dark boxes*: genotypes 1 (Persian vs. Arab, $p=0.035$, Persian vs. Azeri, $p=0.013$), 5 (Bakhtiari vs. Azeri, $p=0.044$), 10 (Persian vs. Arab, $p=0.041$), 12 (Persian vs. Bakhtiari, $p=0.041$), 94 (Persian vs. Arab, $p=0.041$)

Genotype			KIR genes																	Iranian populations							
			Group-A haplotype associated				Group-B haplotype associated							Framework/ Psuedogenes					Number of activating *KIR*s	Persian (n=248)		Bakhtiari (n=96)		Arab (n=76)		Azeri (n=84)	
Number	Haplogroup	Bx Subset	*2DL1*	*2DL3*	*3DL1*	*2DS4*	*2DS2*	*2DL2*	*2DS3*	*2DL5*	*3DS1*	*2DS5*	*2DS1*	*2DP1*	*3DP1*	*2DL4*	*3DL2*	*3DL3*		%F	(N)	%F	(N)	%F	(N)	%F	(N)
5	AB	C4Tx	■	■	■	■	■	■	■	■			■	■	■	■	■	■	3	12.5	(31)	5.2	(5)	14.5	(11)	14.3	(12)
7	AB	C4Tx	■	■	■	■	■	■	■	■	■			■	■	■	■	■	5	4.4	(11)	1.0	(1)	3.9	(3)	3.6	(3)
11	AB	C4Tx	■	■	■	■	■	■	■	■	■			■	■	■	■	■	4	1.6	(4)	1.0	(1)	2.6	(2)	2.4	(2)
10	AB	C4Tx	■	■	■	■	■	■	■	■			■	■	■	■	■	■	4	0.4	(1)			3.9	(3)	2.4	(2)
36*	AB	C4Tx	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	5	0.4	(1)	2.1	(2)			3.6	(3)
61*	AB	C4Tx	■	■	■	■	■	■	■	■				■	■	■	■	■	3	0.4	(1)						
84	BB	C4Tx	■		■	■	■	■	■	■				■	■	■	■	■	3	4.4	(11)	1.0	(1)	1.3	(1)	5.9	(5)
118	BB	C4Tx	■		■	■	■	■	■	■	■		■	■	■	■	■	■	5	1.2	(3)					1.2	(1)
145*	BB	C4Tx		■	■	■	■	■	■	■				■	■	■	■	■	3	0.4	(1)	1.0	(1)				
104	BB	C4Tx	■	■			■	■	■	■	■		■	■	■	■	■	■	4	0.8	(2)						
239*	BB	C4Tx	■	■			■	■	■	■			■	■	■	■	■	■	3	0.4	(1)						
103	BB	C4Tx	■		■	■	■	■	■	■		■	■	■	■	■	■	■	5	0.4	(1)						
110	BB	C4Tx	■		■	■	■	■	■	■			■	■	■	■	■	■	4			1.0	(1)				
202*	BB	C4Tx	■	■			■	■	■	■		■		■	■	■	■	■	3					1.3	(1)		
208*	BB	C4Tx	■		■	■	■	■	■	■		■	■		■	■	■	■	5					1.3	(1)		
108	BB	C4Tx	■		■	■	■	■	■	■	■			■	■	■	■	■	4							2.4	(2)
215*	BB	C4Tx	■	■		■	■	■	■	■	■		■	■	■	■	■	■	5							1.2	(1)
126	BB	C4Tx			■	■	■	■	■	■				■	■	■	■	■	3							1.2	(1)
120	BB	C4Tx	■	■		■	■	■	■	■	■	■		■	■	■	■	■	5							1.2	(1)
20	AB	C4Tx	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	5			1.0	(1)	2.6	(2)	1.2	(1)
6	AB	C4T4	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	6	3.6	(9)	4.2	(4)	5.3	(4)	5.9	(5)
86	BB	C4T4	■	■			■	■	■	■	■	■	■	■	■	■	■	■	5	1.2	(3)					1.2	(1)
94	BB	C4T4	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	6	0.4	(1)			3.9	(3)		
87	BB	C4T4	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	6			5.2	(5)	3.9	(3)		
96	BB	C4T4	■				■	■	■	■	■	■	■	■	■	■	■	■	5	0.8	(2)						
2	AB	CxT4	■	■	■	■				■	■	■	■	■	■	■	■	■	4	8.9	(22)	6.3	(6)	2.6	(2)	3.6	(3)
3	AB	CxT4	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	5	3.6	(9)	5.2	(5)			2.4	(2)
23	AB	CxT4	■	■	■	■			■	■	■	■	■	■	■	■	■	■	5	1.6	(4)					1.2	(1)
18	AB	CxT4	■	■	■	■		■		■	■	■	■	■	■	■	■	■	4	1.2	(3)	1.0	(1)				
47*	AB	CxT4	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	5			1.0	(1)			1.2	(1)
99	BB	CxT4	■	■		■				■	■	■	■	■	■	■	■	■	4			1.0	(1)	6.6	(5)	2.4	(2)
95	BB	CxT4	■	■		■	■	■		■	■	■	■	■	■	■	■	■	5			1.0	(1)	1.3	(1)	1.2	(1)
91	BB	CxT4			■			■		■	■	■	■		■	■	■	■	5			3.1	(3)				
85	BB	CxT4	■	■						■	■	■	■	■	■	■	■	■	3			1.0	(1)				
221*	BB	CxT4		■	■	■	■	■		■	■	■	■		■	■	■	■	5			1.0	(1)				
154	BB	CxT4	■		■	■				■	■	■	■	■	■	■	■	■	4					1.3	(1)		
1	AA	-	■	■	■	■								■	■	■	■	■	1	28.7	(71)	25.0	(24)	15.8	(12)	14.3	(12)
17	AB	CxTx	■	■	■	■			■	■	■	■		■	■	■	■	■	3			1.0	(1)			2.4	(2)
25	AB	CxTx	■	■	■	■	■	■		■	■	■		■	■	■	■	■	4			2.1	(2)				
214*	BB	CxTx	■	■		■			■	■	■	■		■	■	■	■	■	4							1.2	(1)
4	AB	CxTx	■	■	■	■	■	■						■	■	■	■	■	2	8.5	(21)	8.4	(8)	11.9	(9)	5.9	(5)
16	AB	CxTx	■	■	■	■			■	■	■			■	■	■	■	■	3	0.4	(1)	2.1	(2)	1.3	(1)		
15	AB	CxTx	■	■	■	■						■	■	■	■	■	■	■	2	0.4	(1)	2.1	(2)	2.6	(2)		
8	AB	CxTx	■	■	■	■			■	■	■			■	■	■	■	■	4	0.8	(2)			3.9	(3)	1.2	(1)
22	AB	CxTx	■	■	■	■	■	■		■				■	■	■	■	■	2	2.8	(7)	1.0	(1)			1.2	(1)
9	AB	CxTx	■	■	■	■	■	■		■		■	■	■	■	■	■	■	4	1.6	(4)					4.8	(4)
48*	AB	CxTx	■	■	■	■	■	■		■	■		■	■	■	■	■	■	4	0.8	(2)					1.2	(1)
24	AB	CxTx	■	■	■	■	■	■		■			■	■	■	■	■	■	3	0.4	(1)					1.2	(1)
12	AB	CxTx	■	■	■	■					■		■	■	■	■	■	■	2	0.4	(1)	4.1	(4)				
42	AB	CxTx	■	■	■	■	■	■	■				■	■	■	■	■	■	3	0.4	(1)	1.0	(1)				
26	AB	CxTx	■	■	■	■				■		■	■	■	■	■	■	■	3	0.4	(1)	1.0	(1)				
54*	AB	CxTx	■	■	■	■	■	■			■			■	■	■	■	■	3			1.0	(1)	2.6	(2)		
43	AB	CxTx	■	■	■	■							■	■	■	■	■	■	1			1.0	(1)			1.2	(1)
57	AB	CxTx	■	■	■	■		■	■	■	■			■	■	■	■	■	3	0.4	(1)						
46	AB	CxTx	■	■	■	■	■	■				■		■	■	■	■	■	3	0.4	(1)						
29	AB	CxTx	■	■	■	■						■		■	■	■	■	■	2	0.4	(1)						
44	AB	CxTx	■	■	■	■		■	■	■	■			■	■	■	■	■	4	0.4	(1)						
59*	AB	CxTx	■	■	■	■		■		■	■			■	■	■	■	■	3	0.4	(1)						
32	AB	CxTx	■	■	■	■		■	■					■	■	■	■	■	2	0.4	(1)						
60*	AB	CxTx	■	■	■	■									■	■	■	■	1	0.4	(1)						
19	AB	CxTx	■	■	■	■		■						■	■	■	■	■	1			2.1	(2)				
56	AB	CxTx	■	■	■	■	■	■			■		■	■	■	■	■	■	4			1.0	(1)				
74*	AB	CxTx	■	■	■	■	■	■		■		■	■	■	■	■	■	■	4					1.3	(1)		
13	AB	CxTx	■	■	■	■	■							■	■	■	■	■	2							3.6	(3)
76*	AB	CxTx	■	■	■	■		■	■					■	■	■	■	■	2							1.2	(1)
102	BB	CxTx	■		■	■	■	■						■	■	■	■	■	2	0.8	(2)						
112	BB	CxTx			■	■	■	■		■		■	■		■	■	■	■	4	0.4	(1)						
240*	BB	CxTx	■		■	■	■	■				■	■	■	■	■	■	■	3	0.4	(1)						
241*	BB	CxTx		■	■	■	■	■							■	■	■	■	2	0.4	(1)						
88	BB	CxTx			■	■	■	■							■	■	■	■	2	0.4	(1)						
100	BB	CxTx	■	■					■	■	■			■	■	■	■	■	3	0.4	(1)						
220*	BB	CxTx		■	■	■	■	■						■	■	■	■	■	3			1.0	(1)				
219*	BB	CxTx	■						■		■			■	■	■	■	■	2			1.0	(1)				
218*	BB	CxTx	■		■	■	■	■						■	■	■	■	■	2			1.0	(1)				
101	BB	CxTx	■		■	■	■	■		■		■		■	■	■	■	■	4					1.3	(1)		
213*	BB	CxTx	■		■	■	■	■		■		■		■	■	■	■	■	3					1.3	(1)		
122	BB	CxTx	■	■		■	■			■		■		■	■	■	■	■	3					1.0	(1)		
217*	BB	CxTx	■	■		■	■			■		■		■	■	■	■	■	3							1.2	(1)
Total genotypes found in each population																				45		36		25		33	

Data analysis and statistical methods

The percentage of individuals carrying each *KIR* gene in four population groups was determined by direct counting (individuals positive for the gene divided by the individuals tested per population×100). Frequencies of A and B haplotypes were calculated using the following formula: group A=$2n_{AA}+n_{AB}/2N$ and group-B=$2n_{BB}+n_{AB}/2N$, where n_{AA}, n_{AB}, and n_{BB} were the numbers of AA, AB, and BB genotypes and N was the total number of individuals tested. Differences between populations in the frequencies of individuals carrying each *KIR* gene and genotype were estimated by two-tailed Fisher exact probability (p) test, and $p<0.05$ was considered to be statistically significant. The principal components analysis (PCA) of carrier frequency of *KIR* genes was carried out using the Minitab statistical software.

Results

Frequency of activating *KIR* gene carriers differ among Iranian populations

All 16 known *KIR* genes were detected in each of the native Iranian populations analyzed in this study, and the frequencies of individuals carrying each *KIR* gene were compared in Table 1. Four framework *KIR* genes (*2DL4, 3DL2, 3DL3* and *3DP1*) were detected in all 504 individuals analyzed in this study. Overall, the A haplotype associated *KIR* genes occurred more frequently than the B haplotype associated *KIR* genes, and their frequencies were comparable between populations. Arab and Azeri revealed similar carrier frequency of each *KIR* gene but differed considerably from those of Persian and Bakhtiari populations (Table 1). Particularly, the carriers of *KIR2DL5*, *2DS2*, and *2DS3* were more in Arab and Azeri populations compared to the Persian and Bakhtiari populations. The carriers of *KIR3DS1* and *2DS5* occurred most frequently in Bakhtiari, and the difference was statistically significant in comparison with Persian population.

The carrier frequency of variably occurring *KIR* genes in four Iranian populations were compared with those reported in other ethnic populations using the PCA analysis (Fig. 2). Apart from a few outliers, distinct geographic clusters of Africans, Northeast Asians, Mexicans, American Natives, Asian Indians, and Caucasians were noticed on the PCA plot (Fig. 2). Four Iranian populations studied in this paper were mapped somewhat close to each other but considerably isolated from the Northeast Asians, Mexicans, and American Natives. Bakhtiari was plotted within the Caucasian group, while Persian was mapped between Caucasian and African groups. Iranian Arab was more closely clustered to the Maharashtrians, a Western Indian population than the Palestine Arab. Azeri stood isolated and revealed some affinity to the Iranian Arab.

Each Iranian population displays distinct *KIR* gene content diversity

Within the study panel of 504 unrelated Iranians, we found 78 distinct *KIR* gene content profiles (genotypes) carrying a different number and combination of 16 *KIR* genes (Fig. 3). Only 10% of these genotypes (1, 2, 4–7, 11, and 84) were observed in all four Iranian populations, but their combined frequencies were 72.6% in Persian, 52.1% in Bakhtiari, 57.9% in Arab, and 55.9% in Azeri. Comparison with other ethnic populations revealed that only Caucasian populations carried all of these eight *KIR* genotypes, and their combined frequencies were comparable to those observed in Iranian populations (Supplement Figure 1a, b). Genotype 1, the homozygous combination of A haplotypes, occurred most frequently in Persian (28.7%), Bakhtiari (25%), and Arab (15.8%; Fig. 3). This is the only genotype found in all ethnic populations investigated to date, and its highest occurrence was reported in the Northeast Asians (Jiang et al. 2005; Whang et al. 2005; Yawata et al. 2002b) (Supplement Figures 1a, b). In Azeri, genotypes 1 and 5 occur at similar frequencies, 14.3% each. Genotype 5 was the second most common profile in Persian (12.5%) and Arab (14.5%), while it occurred only 5.2% in Bakhtiari populations.

The majority of the genotypes characterized in this study (43/78, 55%) were unique to one of the four Iranian populations, and their combined frequency in the entire study panel was 11.9% (Fig. 3). Eighteen of these 43 unique genotypes (59–61, 74, 76, 202, 208, 213–215, 217–221, and 239–241) were not reported in other ethnic populations studied previously (Supplement Figures 1a, b). Five genotypes (36, 47, 48, 54, and 145) that occurred in more than one Iranian population were also not reported in other ethnic populations. Therefore, a set of 23 *KIR* genotypes appeared to be unique to the Iranians and are yet to be detected in other populations (Fig. 3 and Supplement Figures 1a, b).

Nearly 75% of the Iranian Arab and Azeri carry a B *KIR* haplotype

Of the 78 observed genotypes, 40 were predicted to be the heterozygous combination of A and B haplotypes (AB genotypes), 37 were predicted to be the homozygous combination of B haplotypes (BB genotypes), and one was the homozygous combination of A haplotype (AA genotypes; Fig. 3). Over 55% of each Iranian population carried AB genotypes with the highest prevalence in Azeri (65.5%; Table 2). The predicted A haplotypes occurred more frequently than the B haplotypes in Persian and

Table 2 Comparison of genotypes, haplotypes and linkage groups in four Iranian populations

Types	Persian (Per) n=248	Bakhtiari (Bak) n=96	Arab (Arb) n=76	Azeri (Aze) n=84	Per vs. Bak	Per vs. Arb	Per vs. Aze	Bak vs. Arb	Bak vs. Aze	Arb vs. Aze
	%F (N)	%F (*N*)	%F (N)	%F (N)						
AA genotype	28.7 (71)	25.0 (24)	15.8 (12)	14.3 (12)		0.035	0.013			
BB genotypes	12.8 (32)	18.3 (18)	24.6 (19)	20.2 (17)		0.0132				
AB genotypes	58.4 (145)	55.8 (54)	59.1 (45)	65.5 (55)						
C4Tx genotypes	27.4 (68)	13.5 (13)	31.6 (24)	40.5 (34)	0.0068		0.028		0.000043	
CxT4 genotypes	15.3 (38)	20.8 (20)	11.8 (9)	11.9 (10)						
C4T4 genotypes	6.0 (15)	9.3 (9)	13.1 (10)	7.1 (6)						
CxTx genotypes	22.5 (56)	31.2 (30)	27.3 (21)	26.1 (22)						
A haplogroups	57.6 (286)	53.1 (102)	44.7 (68)	46.4 (78)		0.0053	0.012			
B haplogroups	42.3 (210)	46.8 (90)	55.2 (84)	53.5 (90)		0.0053	0.012			
C4 gene-cluster	33.5 (83)	23.0 (22)	44.7 (34)	47.6 (40)			0.026	0.0031	0.00056	
T4 gene-cluster	21.4 (53)	30.2 (29)	25.0 (19)	19.0 (16)						

The haplotype A and B were determined by using the following formula: group A=$2N_{AA}+N_{AB}/2n$ and group B=$2N_{BB}+N_{AB}/2n$, where N_{AA}, N_{AB}, and N_{BB} are the numbers of AA, AB, and BB genotypes, n=total number of individual.

Bakhtiari, and the extreme of this scenario was reported in Northeast Asians (Jiang et al. 2005; Whang et al. 2005; Yawata et al. 2002b; Supplement Figures 1a, b). In contrast, predicted B haplotypes occurred more frequently in Arab and Azeri compared to the A haplotypes (Table 2). This scenario was previously observed in the natives of America, India, and Australia (Gendzekhadze et al. 2006; Norman et al. 2002; Rajalingam et al. 2008; Toneva et al. 2001).

Nearly half of the Iranian Arab and Azeri populations carried *KIR2DS2-2DL2-2DS3-2DL5* gene cluster

All four Iranian populations investigated in these study carried all four subsets of Bx genotypes (CxT4, C4Tx, C4T4, and CxTx), while some ethnic populations studied previously lacked one or more of these subsets (Fig. 4). Within our study panel of 504 Iranians, individuals displaying C4Tx genotypes carried three to five activating *KIR* genes (61.9% carried three activating *KIR*s), while individuals displaying CxT4 genotypes carried three to five activating *KIR* genes (59.0% carried four activating *KIR*s), individuals displaying C4T4 genotypes carried five to six activating *KIR* genes (75.5% carried six activating *KIR*s), and individuals displaying CxTx carried one to four activating *KIR*s (60.2% carried two activating *KIR*s). The Azeri (40.5%), Arab (31.6%), and Persian (27.4%) comprised the higher frequencies of Bx genotypes with C4Tx configuration compared to any other population studied thus far (Fig. 4). Interestingly, the C4Tx subset was virtually absent from American natives, in whom CxT4 occurred predominantly at a frequency of 70%. In Bakhtiari, the Bx genotypes missing C4 and T4 gene clusters (CxTx) were more common compared to the other three Iranian populations. Overall, the constellation of Bx genotypes of Iranians was comparable to Asian Indians and Caucasians but differed substantially from the American natives, Northeast Asians, and Africans (Fig. 4).

Discussion

Persian and Bakhtiari populations were the descendants of ancient Elamites and Aryans, who arrived in parts of Greater Iran from central Asia in the second millennium BC. Genetic studies describing mitochondrial DNA (mtDNA) sequence variation, Y chromosome SNP, and HLA gene polymorphism revealed close affinities among Persian, Bakhtiari, and European Caucasian populations (Farjadian et al. 2009; Nasidze et al. 2008). Consistent with the ethnic ancestry and genetic homology, the *KIR* gene content diversity determined in Bakhtiari and Persian populations were comparable to those reported in Caucasian populations and revealed a balance of A and B *KIR* haplotypes. Compared to the Bakhtiari and Caucasian populations, the Persian displayed a higher frequency of genotype 5, which lacks T4 gene cluster (*KIR3DS1, 2DS5* and *2DS1* genes). The genotype 5 occurred most frequently in African populations (Denis et al. 2005; Du et al. 2007; Norman et al. 2002) but is completely absent in American natives (Ewerton et al. 2007; Flores et al. 2007; Gendzekhadze et al. 2006). Unlike the Bakhtiari, a nomadic pastoralist tribal group that straddles the central Zagros Mountains in the province of Khuzistan, the Persian had several historical admixtures, which presumably is the source for the high incidence of genotype 5.

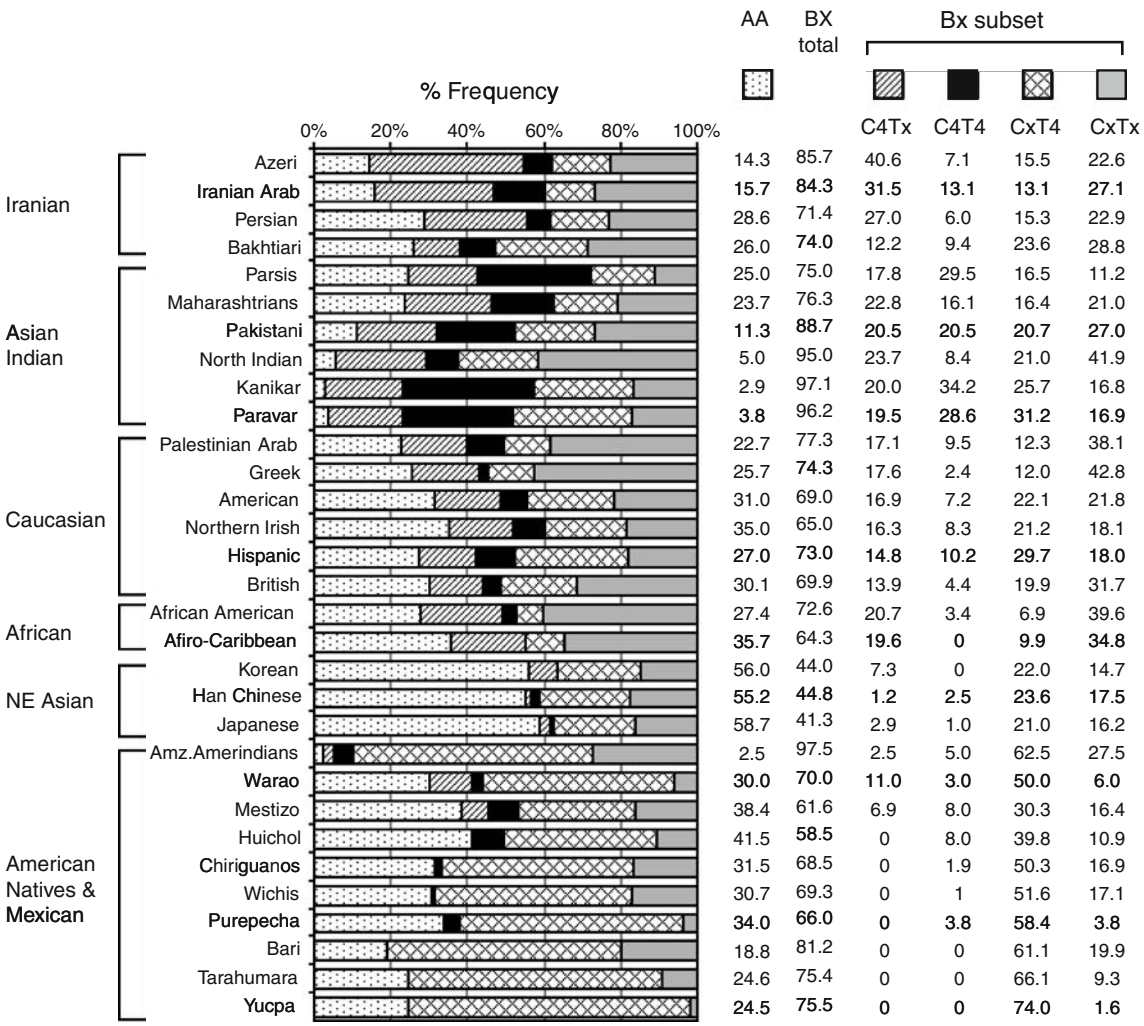

Fig. 4 Subsets of *KIR* gene content profiles and their frequency in populations. The frequencies of distinct *KIR* genotype subsets in four Iranian populations are shown in comparison with other previously studied populations. The individuals carrying *KIR3DL3-2DL3-2DL1-2DP1-3DP1-2DL4-3DL1-2DS4-3DL2*, a fixed gene content characteristic of A haplotypes, were considered to have *AA* genotypes (two copies of A haplotypes). Remainders carried Bx genotypes, which comprised either one copy of A haplotype and one copy of B haplotype (*AB* genotypes) or two copies of B haplotypes (*BB* genotypes). Based on the presence and absence of two distinct gene clusters (C4, *KIR2DS2-2DL2-2DS3-2DL5*; T4, *KIR3DS1-2DL5-2DS5-2DS1*), the Bx genotype carries were divided into four subsets: C4Tx (presence of C4 and absence of T4), CxT4 (absence of C4 and presence of T4), C4T4 (presence of both C4 and T4), CxTx (absence of both C4 and T4)

Compared to the geographic neighbors, a greater variability was recently observed at the *KIR* locus in Indian Parsi, a descendent of Iranian Zoroastrians who emigrated to Western India in the seventh century AD (Kulkarni et al. 2008). Notably, the Indian Parsi had a significantly higher frequency of *KIR3DS1* than did the Northern Indian populations, and possible evolutionary pressure was suggested to retain such high frequency of *KIR3DS1* in Indian Parsi. The Y chromosome SNP data showed that the Parsis of India resembled Iranian populations rather than their Indian neighbors (Qamar et al. 2002). *KIR* gene content diversity data of native Iranian populations was not available at that time for comparison. Herein, we compared the Indian Parsi data with those of other world populations, including four native Iranian populations characterized in this study and three Southern Indian tribal populations studied recently (Rajalingam et al. 2008). The analyses revealed that the *KIR* gene content profiles of Indian Parsi were more comparable to the Indian populations than the native Iranians. Specifically, 29.5% of Parsis of India were the carriers of C4T4 Bx genotypes, while only 6% of the Persian displayed this constellation. Consequently, the Parsis of India comprised more activating *KIR* genes than the Iranian Persian. It is intriguing to postulate that the Parsis of India gained the C4 (*KIR2DS2-2DL2-2DS3-2DL5*) and T4 (*KIR3DS1-2DL5-2DS5-2DS1*) gene clusters by accumulating the activating *KIR* genes during their migration to India or following their settlement in India through population bottlenecks and episodes of selection by infectious disease.

The Iranian Arab population mainly occupies the Khuzestan province of Iran. Historical evidence indicates that their ancestors, Arab tribes such as the *Bakr bin Wael* and *Bani Tamim*, entered Iran in the seventh century AD, although there may have been an earlier Arabic presence in Iran (Morony 2006). The mtDNA HV1 sequence polymorphisms and Y chromosome bi-allelic diversity showed that the North African Arabs were far more distant genetically from the Iranian Arab (Nasidze et al. 2008). Moreover, the Iranian Arab shared close relatedness to the neighboring geographic groups. Haplogroups J2 and G were especially intriguing because they were found in very high frequencies in Bakhtiari and Iranian Arab (Nasidze et al. 2008). Despite the genetic affinity and geographic proximity, the Iranian Arab carried the highest frequency of B haplotypes among the four Iranian populations, while the Bakhtiari displayed a balance of A and B haplotypes. Intriguingly, the *KIR* genomic diversity of Iranian Arab was more similar to the Indian Maharashtrians and Iranian Azeri than the Palestinian Arab. Particularly, the Iranian Arab, Azeri, and Indian Maharashtrians displayed a comparable constellation of Bx genotypes with high frequencies of the C4 gene cluster (*KIR2DS2-2DL2-2DS3-2DL5*) compared to the Palestinian Arab (Supplement Figure 1b).

Comparative analyses of *KIR* data from world populations revealed a link between the prehistoric human migrations and the evolution of two groups of *KIR* haplotypes distinguished by their content of activating *KIR* genes (Rajalingam et al. 2008). The natives of America, India, and Australia, who had extensive prehistoric migrations, carried high frequencies of *B* haplotypes, and presumably, they acquired these activating *KIR* enriched haplotypes to survive different environmental challenges on their journey. The natives of India and Australia were considered to be the most ancient human dispersal out of Africa, which happened about 60,000 years ago, most likely via the tropical coast of the Arabian peninsula, India, Southeast Asia, and Australia. An increasing frequency cline of B haplotypes from Arabs (51.8% in Palestinian Arab and 55.3% in Iranian Arab) toward Pakistani (60.5%), Indian tribes (~70%), and Australian aborigines (>70%) suggests that the expansion of B haplotypes in the most ancient migratory group began in Arabian peninsula that bridges Africa and Asia.

Azeri, one of the major Iranian ethnic populations that speaks an Indo-European language, has mixed genetic (mtDNA and Y chromosome) and cultural elements of Persian, Caucasian, and Turkic people (Ashrafian-Bonab et al. 2007; Nasidze et al. 2003; Quintana-Murci et al. 2004). However, by displaying a dominance in B *KIR* haplotypes that carry C4 gene cluster (*KIR2DS2-2DL2-2DS3-2DL5*), the Azeri population was more related to Iranian and Indian populations. It is not clear whether a local specific selection or a racial admixture is responsible for the dominance of B haplotypes in Azeri. In conclusion, the genetic pool supplied by the waves of prehistoric migration, subsequent racial admixture, and local-specific selection appeared to be the force that determined the *KIR* diversity in modern Iranians.

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